

### REMARKS

Applicants respectfully requests reconsideration and allowance of all pending claims.

#### Status of the Claims

In this Amendment D, claims 1, 6, 10 and 24 have been amended, and new claim 27 added, to more particularly claim certain preferred embodiments of the invention. Additionally, claims 4, 5 and 26 have been cancelled. Accordingly, claims 1, 3, 6, 8, 10-25 and 27 will be pending upon entry of this Amendment.

In this Amendment, claims 6 and 10 have been amended by changing their dependencies from cancelled claims 5 and 9, respectfully, to claim 1. With respect to independent claims 1 and 26, it is to be noted that the claims have been amended to require that (1) the stationary phase be bonded-silica containing ligands selected from the group consisting of butyl-, octyl- and octadecyl-moieties, and (2) the pH of the aqueous mobile phase be in the range of from about 2.5 to about 3.5. Support for these amendments may be found in originally filed claims 5 and 9, as well as in the instant specification at paragraphs [0026] and [0028].

Regarding new claim 27, claim 27 requires (1) a step of acidifying the impure aqueous preparation to prepare a fentanyl salt with a pH in the range of about from about 2.5 to about 3.5 and (2) that the stationary phase be bonded-silica containing ligands having octyl-moieties. Support for these features may be found in originally filed claims 1, 6 and 20, as well as paragraph [0026] of the instant specification.

#### Interview Summary

The undersigned attorney thanks the Examiner for the interview that took place between the Examiner, the Examiner's Supervisor (Janet Andres), the undersigned, and Derick Allen (Reg. No. 43,468) of Armstrong Teasdale LLC, on November 10, 2009. The patentability of independent claims 1 and 24 was discussed, and the both the Examiner and Applicant's representatives proposed potential amendments to claims 1 and 24. In particular, it was noted that the Examiner indicated pending claim 1 may be allowable after incorporation of one or more limitations from the dependent claims, and referenced claims 5 and 9 in particular.

### Outstanding Rejections under 35 U.S.C. §103(a)

The Office has maintained its rejection of the pending claims as obvious in view of the disclosures of: US 4,317,903; US 4,234,684; US 4,293,489; US 4,336,333; US 4,904,590; and, US 5,780,589. Applicant submits that independent claims 1 and 24, as well as new independent claim 27, are patentable over the cited references for the reasons of record, and furthermore are patentable for the additional recitations therein;<sup>1</sup> namely, for the requirement that the stationary phase is bonded-phase silica containing ligands selected from the group consisting of butyl-, octyl- and octadecyl-moieties (and octyl-moieties as in the case of claim 27), and for the requirement that the aqueous mobile phase pH is in the range of from about 2.5 to about 3.5. Independent claim 27 is further patentable for its requirement that the impure aqueous preparation is acidified to prepare a fentanyl salt with a pH in the range of from about 2.5 to about 3.5.

Applicant has found that silica based stationary phases containing butyl-, octyl- or octadecyl-moieties are preferred for the removal of phenethylpiperaniline from fentanyl solutions with octyl-moieties being especially preferred (see para. [0026] of the instant specification). Additionally, Applicant has found that it is desirable to maintain the pH of the mobile phase between about 2.5 and about 3.5, as a pH value above about 3.5 may result in unnecessary absorption of fentanyl in the stationary phase and a pH value below about 2.5 may cause degradation of the stationary phase via detachment of the active ligand, resulting in costly replacement or regeneration costs. Applicant respectfully submits that these claim elements are due patentable weight, inasmuch as the Office has not established why one of ordinary skill in the art would arrive at these or that these would be a matter of routine experimentation as set forth below.

The Office contends that many of the recitations of the independent claims and of the dependent claims, such as the stationary phase loading ratio, solid supports and doping acids are routine chromatographic procedures and that when the general conditions of a claim are disclosed in the prior art, it not inventive to discover the optimum or workable ranges by routine experimentation (see p. 5 of the Office action). Applicant submits that (1) the general conditions of independent claims 1, 24 and 27 have not been shown, and (2) the Office has not established that these parameter are **result-effective variables** (i.e., a variable which achieves a recognized result, as required before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation). MPEP §2144.05(II)(B).

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<sup>1</sup> See Applicant's Amendment C, submitted on July 27, 2009, the contents of which are respectfully incorporated herein by reference, but which will not be repeated in full here in the interests of brevity.

In accordance with *In re Aller*, 220 F.2d 454, 105 USPQ 233 (CCPA 1955), cited by the Office, in order to establish that the various parameters at issue are routine experimentation, the Office must show that the other general conditions of the claim are known. For instance, in *In re Aller*, the **only difference** between the prior art and the claimed process was that the claimed process was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% and the prior art process was performed at a temperature of 100°C and an acid concentration of 10%. Regarding the differences between the claimed process for purifying **fentanyl** and the prior art, the Office has failed to establish that the general conditions of the process were known. Indeed, as Applicant has previously pointed out (see, e.g., Applicant's Amendment C), the Office has failed to produce **any reference** in which **fentanyl** is subjected to reverse-phase high-performance preparative liquid chromatography. Furthermore, the Office has failed to produce any reference in which fentanyl is subjected to reverse-phase high-performance preparative liquid chromatography **utilizing the recited stationary phase and mobile phase**. There is simply no guidance in the art regarding suitable ranges for the operating conditions of the separation, including suitable types of media for the stationary phase, media loading rates, elution pH and the like, in order to purify fentanyl in this way.

Moreover, the Office has failed to establish that these parameters are result effective, i.e., that they achieve a recognized result. Such a showing must be made before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation. MPEP §2144.05(II)(B). For instance, the Office has failed to establish that the claimed pH range of about 2.5 to about 3.5 for the aqueous mobile phase would influence the various recovery characteristics, such as the absorption of fentanyl in the stationary phase and the degradation of the stationary phase. Given that the Office has (i) not established the general conditions of removing phenethylpiperaniline from fentanyl solutions (such as, for example, the suitable types of media for the stationary phase, media loading rates and operating pH ranges), and (ii) failed to establish that these parameters are result-effective, the Office has failed to establish a *prima facie* case of obviousness of the pending claims.

In view of the foregoing, Applicant respectfully submits the subject matter of the pending claims is patentable over the cited references. Reconsideration and withdrawal of the present rejections are therefore requested.

#### Double Patenting Rejection

Applicants note that the double patenting rejection has been held in abeyance at this time.

**CONCLUSION**

In view of the foregoing, Applicant respectfully requests favorable reconsideration and allowance of all pending claims. The Commissioner is hereby authorized to charge Deposit Account 13-1160 for any fees due for the submission of this Amendment D, including the fee for a one month extension of time.

Respectfully submitted,

A handwritten signature in black ink, appearing to be 'Craig D. Siman', written over the words 'Respectfully submitted,'.

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